American Journal of Medical Genetics 66:163–168 (1996)

New Form of Bone Dysplasia With Multiple Fractures Associated With Monosomy X

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We report on the clinical, radiologic, and pathologic findings in a 20-week-old fetus with monosomy X and severe hydrops associated with fetal dwarfism. The fetus presented with osteoporosis, bent bones, multiple fractures, and distinctive symmetric submetaphyseal transverse bone interruptions or pseudofractures. We excluded by radiologic and histopathologic examination the diagnoses of osteogenesis imperfecta, hypophosphatasia, campomelic dysplasia, achondrogenesis, hypochondrogenesis, and other types of bone dysplasia. To our knowledge, this is a previously undescribed bone dysplasia associated with monosomy X. This bone dysplasia may be inherited as an X-linked recessive disorder.

KEY WORDS: bone dysplasia, fetus, hydrops, monosomy X, prenatal diagnosis, osteogenesis imperfecta, Turner syndrome

INTRODUCTION

Monosomy X is a chromosomal abnormality frequently encountered in early miscarriages. Intrauterine growth retardation, cervical hygroma, hydrops fetalis, and renal and cardiovascular abnormalities may be detected during pregnancy. Short stature and mild osteoporosis are findings consistently associated with monosomy X.

Short stature, short, deformed tubular bones, and fractures are frequent signs of bone dysplasia that can be detected during pregnancy through fetal ultrasound.

Received for publication July 5, 1995; revision received February 7, 1996.

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We report a very unusual association of monosomy X and short-limb dwarfism with osteoporosis, bent bones, multiple fractures, and submetaphyseal bone interruptions in a 20-week-old fetus.

CLINICAL REPORT

Obstetrical ultrasound at 19 weeks of gestation (WG) of a 30-year-old gravida-1 documented severe fetal hydrops and dwarfism with shortness and bowing of the long bones. No fracture was seen on ultrasound, and there was no polyhydramnios. The father was 34 years old. There was no parental consanguinity or family history of dwarfism, and the pregnancy was otherwise unremarkable. Monosomy X was present in all cells examined. On parental request, an abortion was induced at 20 WG.

On pathological examination, weight was 380 g and foot length 2.5 cm, which are compatible with a gestational age of 17 WG. There was a nuchal mass on the left, with severe generalized subcutaneous edema, especially over the scalp and limbs (Fig. 1). The nuchal mass was cystic, containing relatively clear fluid. There was no evidence of cleft palate, polydactyly, or genital abnormalities. Internal examination showed bilateral pleural effusion and ascites. No visceral malformation was present in the chest or abdomen. However, both lungs were distinctly small, with a combined weight of only 2.9 g. The heart weighed only 0.67 g. The brain weighed 32.2 g (normal weights at 20 GW are 9.1–10 g for the lungs, 2.2–2.4 g for the heart, and 39–46 g for the brain). The ovaries appeared normal. No histologic abnormalities were recognized in the body tissues except for the long bones.

Radiological examination showed a striking excess of soft tissues throughout the body and an overall diminished bone density (Fig. 2). Cranial vault thinning and areas of absent mineralization were the only visible skull abnormalities (Fig. 3). Tooth buds were not seen, as is expected at 20 WG. There was flattening of the vertebral bodies, particularly in the thoracic region. Vertebral body ossification, normally completed by 17 WG, was incomplete in the cervical area (Figs. 2, 4). None of the posterior elements of the spine showed ossification. The 12 pairs of ribs were of normal length

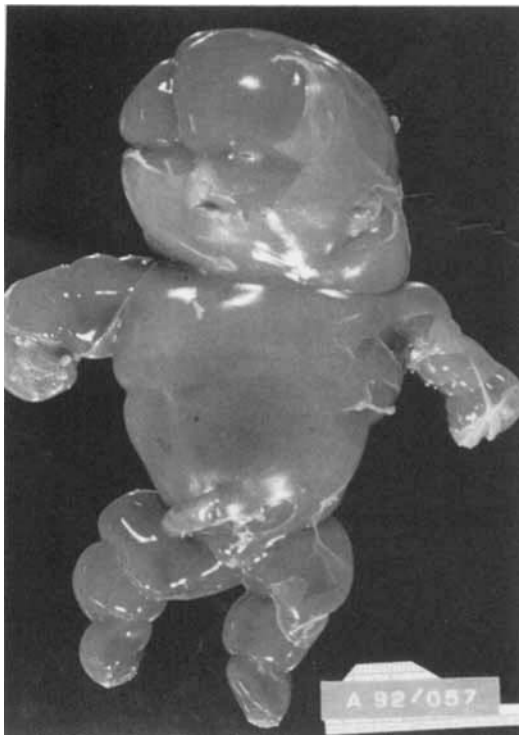

Fig. 1. Severely hydropic fetus.

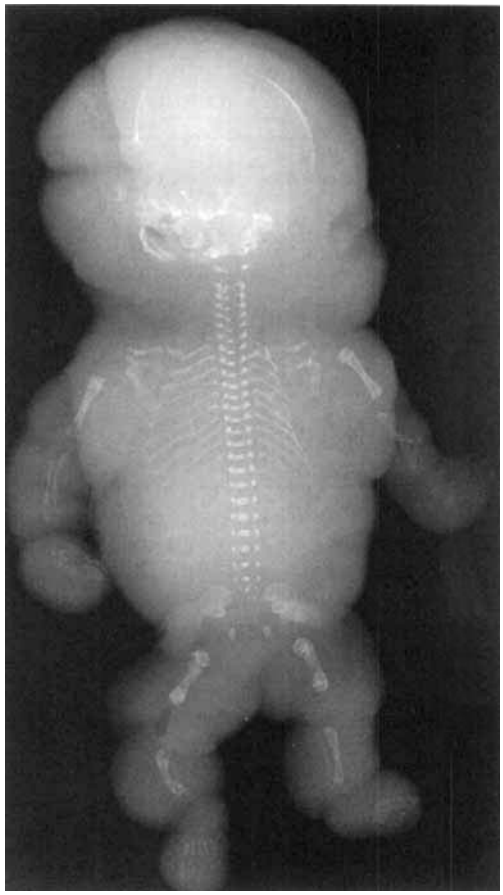

Fig. 2. Anteroposterior (AP) fetal radiogram showing generalized severe hydrops with a large cervical mass, overall diminished bone density, multiple ribs and right clavicle fractures, diaphyseal fractures in the left radius and right ulna, and transverse submetaphyseal interruptions in the proximal humeri, proximal and distal femora, and proximal tibiae. The femora and right tibia are thickened, and all tubular bones appear short, particularly the humeri, femora, and right tibia. The right ulna, left femur, and right tibia also show lateral bowing. Flattening of the upper half of the rib cage is seen on the left side.

but particularly thin and wavy, with deformity and fractures. There was flattening of the upper part of the left rib cage (Fig. 2). Each scapula was shaped like a piece of pie, with a curved medial border, and positioned completely lateral to the upper rib cage (Figs. 2, 4). There was normal ossification of the upper 3 sacral bodies. Iliac bones and ischia were ossified and showed a normal appearance. There was no ossification of the pubic bones, which is probably normal at 20 WG (Fig. 5). Multiple fractures, with no sign of healing, were present in the clavicles, ribs, left radius, and right ulna (Figs. 2, 4). Transverse interruptions in the submetaphyseal region of the tubular bones were clearly seen, suggesting undisplaced transverse fractures or pseudofractures. These were apparent in the proximal humeri, proximal and distal femora, and proximal tibiae. The femora and the right tibia were thick. All tubular bones appeared short, particularly the humeri, femora, and right tibia. The right ulna, left femur, and right tibia also showed lateral bowing. The fibulae were gracile and longer than the tibiae. Ossification centers for the talus and calcaneus had not yet appeared (Figs. 2, 4, 5).

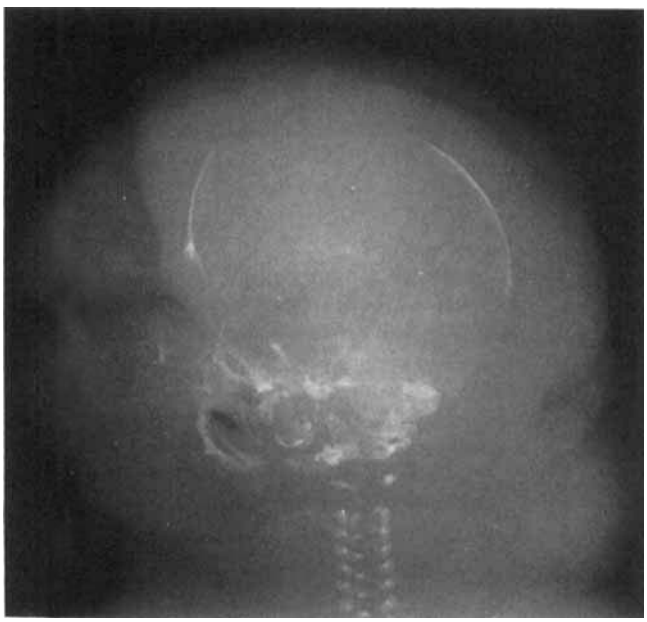

Fig. 3. Enlarged oblique view of the head showing massive scalp thickening, cervical soft tissue mass, and cranial vault thinning with areas of absent mineralization.

Histological studies of the clavicle, humerus, and femur confirmed the radiological appearance of osteopenia with sparse and thin cancellous trabeculae. The epiphyseal cartilage of the long bones was normal. There was deficient ossification of the cartilage spicules

Fig. 4. Enlarged AP radiogram of the right shoulder area showing to better advantage the poorly mineralized, thin, wavy, and fractured right clavicle and ribs and the transverse bone interruption in the proximal humeral metaphysis. The thoracic vertebral bodies are also flat. The scapula is small and triangular, with a curved convex medial border.

at the metaphysis, as seen in osteogenesis imperfecta (OI). However, there was a thick, hypercellular cortical bone toward the midshaft (Fig. 6). Disruption of the cortical surface with metaplastic cartilage, osteoid formation, and osteoclastic activity were seen in the long bones adjacent to the metaphysis (Fig. 7). The hematopoietic component of the bones appeared unremarkable. There were no histopathologic signs of rickets, hypophosphatasia, achondrogenesis, or hypochondrogenesis.

Fig. 5. Enlarged AP radiogram of the pelvis and lower limbs shows to better advantage the findings described in Figure 2. Also noted are the long, gracile fibulae and ossification of the upper 3 sacral bodies.

DISCUSSION

Improvement of fetal ultrasound has resulted in earlier prenatal diagnosis of skeletal dysplasias. This diagnosis can be made as early as 14 WG but is usually made between 16 and 24 WG. The sonographic changes of fetal monosomy X have been described by Brown and Thompson [1984]. Prenatal diagnosis of congenital types of OI and hypophosphatasia, campomelic dysplasia, and achondrogenesis has also been reported [Sharony et al., 1993; Spirt et al., 1990].

Fetal hydrops and growth retardation found in our case are seen with monosomy X. The small heart and lungs are not part of the syndrome but might be explained by the large amount of fluid in the body cavities. Although bone demineralization may result from monosomy X [Smith et al., 1982], fragile bones of the type and severity shown in this fetus have not been described in association with monosomy X. Bone demineralization may indeed explain many radiological changes seen in this fetus, but the short tubular bones, some of which were thick or bowed, the abnormal pie-sector-shaped scapulae, and the distinctive transverse submetaphyseal bone interruptions cannot be secondary to osteopenia.

The differential diagnosis of the bone dysplasia reported here is shown in Table I. It includes OI, hypophosphatasia, achondrogenesis, other types of lethal neonatal dwarfism, and campomelic dysplasia.

OI refers to a group of conditions with predominant signs of osteopenia and increased bone fragility [Bullough et al., 1981; Lachman, 1990; Herman and McAlister, 1991]. As in OI, the case presented here

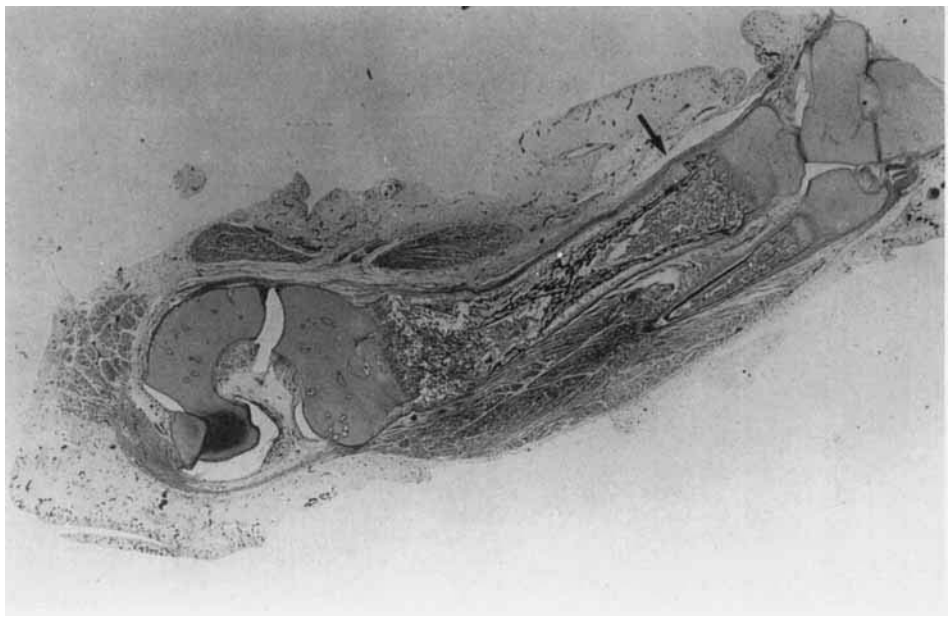

Fig. 6. Microscopic image of the tibia and fibula showing bowing of the long bones, pseudofracture (arrow), and thick cortex at midshaft (×10).

showed nonimmune hydrops and diffuse osteoporosis with undermineralization of the cranial vault and multiple rib and tubular bone fractures with shortening and angulation. However, calcified callus was not seen on the plain radiographs. In addition, the submetaphyseal bone interruptions and the abnormally shaped scapulae are certainly not part of any known OI form and cannot be explained solely by the presence of osteopenia. The histologic changes, as described earlier, are not compatible with OI.

Hypophosphatasia is an inborn error of metabolism characterized by impaired mineralization of the cranial vault and spine and other bones with multiple fractures and ricketslike radiographic changes at the ends of tubular bones [Macpherson et al., 1972]. Marked variability in the degree of bone ossification is also present in hypophosphatasia. Individual verterbrae may show an unusual round or butterfly shape [Macpherson et al., 1972; Shohat et al., 1991]. Diaphyseal skin dimples and bony spurs may be seen [Oestreich and

Fig. 7. Same image as that shown in Figure 6 at a higher magnification (×40). Note the fracture at metaphysis, with metaplastic cartilage formation at the distal end of the tibia. Bony spicules are sparse.

TABLE I. Differential Findings in This Case Compared With Osteogenesis Imperfecta (OI), Hypophosphatemia (HP), Campomelic Dysplasia (CD), Achondrogenesis (ACh), and Hypochondrogenesis (HCh)*

	Propositus	OI	HP	CD	ACh	HCh
Clinical findings						
Hydrops	+	+	−	−	+	−
Dwarfism	+	+	+	+	+	+
Radiological findings						
Osteoporosis	+	+	−	−	−	−
Pseudofractures	+	−	−	−	−	−
Curved bones	+	−	−	+	−	−
Diaphyseal spurs	−	−	+	−	−	−
Cortical bone	Thick	Thin	N	N	N	N
Histology						
Metaplastic cartilage	+	−	−	−	−	−
Rachitic changes at metaphysis	−	−	+	−	−	−
Abnormal endochondral ossification	−	−	−	−	+	−
Hypercellularity (junction cartilage)	−	−	−	−	−	+

*N, normal.

Bofinger, 1989]. Although radiographic similarities to our case are present, including the diffuse bone undermineralization and multiple fractures, the case presented here had no ricketslike radiographic changes, no diaphyseal spurs, and no round or butterfly-shaped vertebral bodies. In addition, our case showed distinctive transverse submetaphyseal bone interruptions in the tubular bones. Bone histology was not diagnostic of hypophosphatasia because there were no rachitic changes in the metaphyses.

Campomelic syndrome is a form of dwarfism associated with anterior bowing and cutaneous dimpling of the lower limbs (femora and tibiae) [Weiner et al., 1976; Houston et al., 1983; Pazzaglia and Beluffi, 1987]. In the case presented here, there were no cutaneous dimples, and only the right tibia and ulna and left femur were visibly bent. In addition, the multiple fractures and the submetaphyseal bone interruptions are not part of campomelic dysplasia, although a fractured femur at the site of bending has been reported in a patient with campomelic dwarfism [Kozlowski et al., 1978]. The craniofacial abnormalities, the hip, elbow and foot deformities, and the thoracic scoliosis often seen in the campomelic dysplasia were not present in our case.

TABLE II. Classification of X-Linked Osteodysplasias[a]

Osteochondrodysplasias	Inheritance
Oto-palato-digital type II	Recessive
X-linked spondyloepiphyseal dysplasia	Dominant
Chondrodysplasia punctata, Conradi-Hünermann type	Dominant
Chondrodysplasia punctata, X-linked type	Recessive
Mucopolysacharidosis type II	Recessive
Metaphyseal anadysplasia	Recessive (?)
Pseudohypoparathyroidism	Dominant (?)
Osteodysplasty, Melnick-Needles	Dominant
Menkes disease	Recessive
Hypophosphatemic rickets	Recessive
Frontometaphyseal dysplasia	Recessive

[a]From the International Working Group on Constitutional Diseases of Bone [1992].

In achondrogenesis [Houston et al., 1972; Slomic and Dorval, 1977; van der Harten et al., 1988], fetal hydrops and poor mineralization, particularly of the vertebral bodies, including the sacrum and ribs, are present. However, in our case, there were completely different radiographic anomalies, e.g., the diffuse osteopenia, cranial vault thinning with areas of absent mineralization, normal ossification of the upper 3 sacral bodies, metaphyseal pseudofractures, and multiple fractures. Histologically, in the lethal forms of achondrogenesis, there is disturbance of endochondrial ossification and meager osteoblastic and osteoclastic activities [Yang et al., 1976], which were not present in our case. The histologic changes of hypochondrogenesis are distinct, with hypervascularity and hypercellularity of cartilage at the chondro-osseous junction [Borochowitz et al., 1986], which were not present in the case reported here.

Other types of bone dysplasias resembling our case have been reported [Astley and Kendall, 1980; Nairn and Chapman, 1989], which also have multiple fractures and metaphyseal transverse bone interruptions. However, the bone density was increased, and there was a very irregular trabecular pattern with some punctate epiphyses. Lethal non-OI bone dysplasia with gracile skeleton and multiple fractures [Kozlowski and Kan, 1988; Maroteaux et al., 1988] can be ruled out in our patient because the long bones were short with relatively thick diaphyses and pseudofractures in the submetaphyseal region.

Monosomy X has been described in association with a number of bone diseases: dyschondrosteosis [Pascual Castroviejo et al., 1977; Suanes Cabello et al., 1993], osseous dystrophy [Louyot et al., 1966], Albright hereditary osteodystrophy [Lieschke et al., 1968], spondyloepiphyseal dysplasialike bone appearance [Nakashima et al., 1990], spondyloepiphyseal dysplasia tarda [Massa et al., 1989], multiple epiphyseal dysplasia [Lowry and Wood, 1977], craniosynostosis [Bozzola et al., 1986; Massa et al., 1987], and achondroplasia [Leonard et al., 1979]. None of these conditions are compatible with the phenotype of our patient. Similarly, this case is not com-

patible with known recessive or dominant X-linked osteodysplasias (Table II).

This association of a new type of bone dysplasia with monosomy X probably is explained by a mutation in an X-linked gene. This syndrome would have remained unrecognized because of early expression and lethality in utero. Other explanations include a new allelic form of a known X-linked bone dysplasia and a fortuitous association of monosomy X with an autosomal dominant or recessive Mendelian condition.

The findings in this fetus do not match those of any reported cases. Thus, we conclude that this is a new and undescribed form of fetal dwarfism. Its distinctive manifestations are the symmetric submetaphyseal transverse bone radiologic interruptions, represented by pseudofractures on radiography and by metaplastic cartilage, deficient healing, and as a hypercellular diaphyseal cortical bone on histopathology. This type of dwarfism may be inherited as an X-linked recessive disorder.

ACKNOWLEDGMENTS

We thank Dr. S. Samuel Yang for his expert opinion and help with the microscopic findings and Dr. C. Stuart Houston for his expert opinion and help with the radiological findings. The technical assistance of France Bernier and Hasu Parikh and the secretarial assistance of Manon St. Pierre and Catherine Prosser is also greatly appreciated.

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